Gene expression changes in the retina following subretinal injection of human neural progenitor cells into a rodent model for retinal degeneration.

Authors: Melissa K Jones, Bin Lu, Mehrnoosh Saghizadeh, Shaomei Wang

Public Summary:

Retinal degenerative diseases (RDDs) affect millions of people and are the leading cause of vision loss. Although treatment options for RDDs are limited, stem and progenitor cell–based therapies have great potential to halt or slow the progression of vision loss. Our previous studies have shown that a single subretinal injection of human forebrain derived neural progenitor cells (hNPCs) into the Royal College of Surgeons (RCS) retinal degenerate rat offers long-term preservation of photoreceptors and visual function. Furthermore, neural progenitor cells are currently in clinical trials for treating age-related macular degeneration; however, the molecular mechanisms of stem cell–based therapies are largely unknown. This is the first study to analyze gene expression changes in the retina of RCS rats following subretinal injection of hNPCs. Functional, biologic, and cellular component analyses indicate that the immune response is enhanced in the untreated RCS rat model and that the subretinal injection of hNPC induce immunomodulation in the retina, either by directly signaling to immune cells or indirectly by aiding in photoreceptor survival thereby inactivating immune cells. The results from this study provide evidence of the gene expression changes that occur following treatment with hNPCs in the degenerating retina. This information can be used in future studies to potentially enhance or predict responses to hNPC and other stem cell therapies for retinal degenerative diseases.

Scientific Abstract:

PURPOSE: Retinal degenerative diseases (RDDs) affect millions of people and are the leading cause of vision loss. Although treatment options for RDDs are limited, stem and progenitor cell-based therapies have great potential to halt or slow the progression of vision loss. Our previous studies have shown that a single subretinal injection of human forebrain derived neural progenitor cells (hNPCs) into the Royal College of Surgeons (RCS) retinal degenerate rat offers long-term preservation of photoreceptors and visual function. Furthermore, neural progenitor cells are currently in clinical trials for treating age-related macular degeneration; however, the molecular mechanisms of stem cell-based therapies are largely unknown. This is the first study to analyze gene expression changes in the retina of RCS rats following subretinal injection of hNPCs using high-throughput sequencing. METHODS: RNA-seq data of retinas from RCS rats injected with hNPCs (RCS(hNPCs)) were compared to sham surgery in RCS (RCS(sham)) and wild-type Long Evans (LE(sham)) rats. Differential gene expression patterns were determined with in silico analysis and confirmed with qRT-PCR. Function, biologic, cellular component, and pathway analyses were performed on differentially expressed genes and investigated with immunofluorescent staining experiments. RESULTS: Analysis of the gene expression data sets identified 1,215 genes that were differentially expressed between RCS(sham) and LE(sham) samples. Additionally, 283 genes were differentially expressed between the RCS(hNPCs) and RCS(sham) samples. Comparison of these two gene sets identified 68 genes with inverse expression (termed rescue genes), including Pdc, Rp1, and Cdc42ep5. Functional, biologic, and cellular component analyses indicate that the immune response is enhanced in RCS(sham). Pathway analysis of the differential expression gene sets identified three affected pathways in RCS(hNPCs), which all play roles in phagocytosis signaling. Immunofluorescent staining detected the increased presence of macrophages and microglia in RCS(sham) retinas, which decreased in RCS(hNPCs) retinas similar to the patterns detected in LE(sham). CONCLUSIONS: The results from this study provide evidence of the gene expression changes that occur following treatment with hNPCs in the degenerating retina. This information can be used in future studies to potentially enhance or predict responses to hNPC and other stem cell therapies for retinal degenerative diseases.